The Novel IL-2 Cytokine Immune Agonist NKTR-214 Harnesses the Adaptive and Innate Immune System for the Treatment of Solid Cancers

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BACKGROUND
- NKTR-214 is a CD122-biased cytokine agonist conjugated with multiple releasable chains of polyethylene glycol (PEG) designed to provide sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2R) to preferentially activate and expand effector CD8+ T and NK cells over Tregs (Figure 1).

NKTR-214 MONOTHERAPY STUDY
- A phase 1, multicenter, open-label, dose-escalation study (EXCEL) was conducted to assess the safety, preliminary efficacy, pharmacokinetics, and pharmacodynamics of NKTR-214 in 28 patients with locally advanced or metastatic solid tumors.
- Outpatient regimen with a convenient IV dosing regimen every 2 or 3 weeks.
- NKTR-214 has a favorable safety and tolerability profile.
- No evidence of immune-mediated AEs or organ related inflammation (e.g., colitis, pneumonitis, dermatitis, hepatitis, endocrinopathies).
- Grade 3 hypotension occurred in 14% of patients and was rapidly reversible with IV fluids.
- No patients experienced capillary leak syndrome.
- No Grade 4 TRAEs or treatment-related deaths
- Maximum-administered dose (MAD) was 0.012 mg/kg.
- Sustained exposure and robust PD changes after a single dose of NKTR-214 (Figure 3).
- NKTR-214 substantially increased CD8+ T cells that were newly proliferative (Ki-67+) (Figure 4).

RESULTS
- NKTR-214 induces activating markers and co-inhibitory receptors in proliferating CD4+ T cells in peripheral blood (Figure 5).
- NKTR-214 induces activating markers and co-inhibitory receptors in proliferating CD8+ T cells in peripheral blood (Figure 6).

CONCLUSIONS
- Immunological activity in peripheral blood and tumor tissue consistent with NKTR-214’s biological mechanism of biased IL-2 pathway activation.
- NKTR-214 has a robust PK-PD profile.
- Robust immune-stimulatory response in the tumor and blood.
- NKTR-214 induced change in proliferative index of immune cells and costimulatory/checkpoint markers only on newly proliferating immune cells.
- RNA expression changes consistent with increased immune cell infiltrate and activation of effector mechanisms.
- Increased frequency of specific T cell clones and associated increase in T cell repertoire suggest efficient remodeling of the T cell repertoire.
- The ability of NKTR-214 to increase TILs and increase PD-1 expression on immune cells provides a sound biological basis for combination with anti-PD1 checkpoint inhibitors.
- Clinical trials currently enrolling patients with NKTR-214 in combination with anti-PD1 checkpoint inhibitors.

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REFERENCES
- Available at: http://ir.nektar.com/events.cfm

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